Introduction to Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide

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Background

When making health care decisions, patients, health care providers, and policymakers routinely seek unbiased information about the effects of treatment on a variety of health outcomes. Nonetheless, it is estimated that more than half of medical treatments lack valid evidence of effectiveness,[1-3] particularly for long-term and patient-centered outcomes. These outcomes include humanistic measures such as the effects of treatment on quality of life, which may be among the most important factors that affect patients' decisions about whether to use a treatment. In addition, therapies that demonstrate efficacy in well-controlled experimental settings like randomized controlled trials may perform differently in general clinical practice, where there is a wider diversity of patients, providers, and health care delivery systems.[4-5] The effects of these variations on treatment are sometimes unknown but can significantly influence the net benefits and risks of different therapy options in individual patients.

Moreover, efficacy studies designed to optimize internal validity often make tradeoffs with respect to external validity or the generalizability of the results to patients, providers, and settings that are different from those which were studied. The absence of patient-relevant and unbiased information about the effectiveness of treatments across the range of potential users can create uncertainty about what outcomes will occur in different patient populations who seek care in general practice. Unfortunately, the lack of relevant information is often highest for patient groups with the greatest need for health care, such as the elderly, people with disabilities, or people with complex health conditions. Uncertainty about the effects of treatment on patient outcomes may lead to the overuse of ineffective or potentially harmful therapies, the underuse of effective therapies, and empiric treatment or off-label use for conditions for which the therapies have not been rigorously studied; the latter situation may be a risky gamble, since the true balance of treatment harms and benefits may be unknown or poorly understood.

In addition, new drugs and other interventions often lack comparative efficacy data to quantify a therapy's equivalence or superiority to existing treatments.[6] This lack of information contributes to the uncertainty about whether a new therapy will be better, worse, or the same as existing treatment options. In some cases, it may also positively skew patient or provider demand in favor of newer therapies and technologies because of expectations that these therapies are inherently better than those that are already available. An artificially high demand for new technologies creates a conundrum for society, which seeks to foster innovation and the development of substantially better therapies—while avoiding the harms and inefficient use of resources that occurs when ineffective or harmful therapies are used in patients who receive little or no benefit.

In the United States and internationally, decisions based on the principles of evidence-based health care have guided health care practice, education, and policy for more than 25 years.[7] The core principles of evidence-based health care are that decisions should be made using the best available scientific evidence in light of an individual patient and that patient's values. At the policy level, these decisions are usually focused on specific populations, such as Medicare or Medicaid enrollees, and may include considerations about costs and the availability of resources. Evidence is usually derived from critical appraisal of all relevant research, as is done in a systematic review of the literature. Evidence is generally considered strong when appraised studies show consistent results, are well designed to minimize bias, and are from representative patient populations. Treatment decisions are generally guided by assessing the certainty that a course of therapy will lead to the outcomes of interest to the patient, and the likelihood that this conclusion will be affected by the results of future studies.

High-quality research can reduce uncertainty about the net benefits of treatment by providing scientific evidence and other objective information for informing health care decisions. As findings from well controlled studies are published in the health care literature, knowledge accumulates about the effects of treatment on health outcomes in different patient populations and settings of care. This knowledge can be used to inform patient decisionmaking so that the most appropriate treatment for an individual patient is provided. Yet it is rare that any one study addresses all dimensions of a health care issue, and there are often knowledge gaps in areas where no research has been conducted. Likewise, some published findings may be flawed or have biases that limit or invalidate its conclusions. In both cases, knowledge gaps and poor quality research restrict the conclusions that may be drawn based on the evidence base. This requires that patients, other stakeholders, systematic reviewers, and researchers work collaboratively to develop new studies and programs of research that can be used to inform the most important decisions facing patients about their health care.

Recognizing the need for outcomes research, Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) authorized AHRQ in 2003 to conduct studies designed to improve the quality, effectiveness, and efficiency of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).[8] The essential goals of Section 1013 are to develop and disseminate valid scientific evidence about the comparative effectiveness of different treatments and appropriate clinical approaches to difficult health problems. To implement Section 1013, AHRQ established the Effective Health Care (EHC) Program, which supports a variety of activities aimed at synthesizing, generating, and disseminating scientific evidence to patients, providers, and policymakers.[9] Subsequent legislation, including the American Recovery and Reinvestment Act of 2009 and the Patient Protection and Affordable Care Act of 2010 (ACA), provided expanded legislative provisions for AHRQ to conduct comparative effectiveness and patient-centered outcomes research. In addition, the ACA established a new nongovernmental research institute, the Patient-Centered Outcomes Research Institute (PCORI). The Institute is an independent organization created to sponsor research that can be used to inform health care decisions. The ACA includes statutory roles for AHRQ and the National Institutes of Health in PCORI, providing a unique relationship for collaboration between government and nongovernment entities.

A component of AHRQ's EHC Program that is devoted to the generation of new scientific evidence is the DEcIDE Research Network. DEcIDE is an acronym for Developing Evidence to Inform Decisions about Effectiveness. It is a collaborative research program that currently involves 11 research centers.[10] These centers primarily focus on conducting observational CER studies and methodological activities in collaborations with patients, other stakeholders, and AHRQ. Through the DEcIDE Network, new scientific evidence is developed to address knowledge gaps that are critical to improving the quality, effectiveness, and efficiency of health care delivered in the United States. Examples of research that has been produced through the DEcIDE Network include examinations of the health outcomes of drug-eluting stent implantation,[11] antipsychotic medication use in the elderly,[12] medication use in chronic obstructive pulmonary disease,[13] carotid revascularization among Medicare beneficiaries,[14] prescription drugs in pregnancy,[15] ADHD treatment in children[16] and adults,[17] radiation therapy in the treatment of prostate cancer,[18] and research methods.[19-20]

Aims of the User's Guide Related to the Design of Observational CER Protocols

The goal of the AHRQ DEcIDE Program is to generate scientific evidence that improves knowledge and informs decisions about the outcomes and effectiveness of health care. Evidence is generated by supporting the development of scientifically rigorous research that is designed to produce new knowledge and reduce uncertainty about the effects on patient health outcomes of treatments, prevention, or other interventions. One of the most important components of research design is the creation of a

study protocol, which is the researchers' blueprint to guide and govern all aspects of how a study will be conducted. A study protocol directs the execution of a study to help ensure the validity of the final study results. It also provides transparency as to how the research is conducted and improves the reproducibility and replicability of the research by others, thereby potentially increasing the credibility and validity of a study's findings.

For studies designed as randomized clinical trials, research protocols are common and standards have been developed for the content of these protocols. However, for other study designs, such as observational research, there are few standards specifically for what elements are recommended for inclusion in a study protocol. As a result, there is a wide range of practices among investigators.[21] Research financially supported through grant or contract funding is usually awarded based on a study proposal or grant application, which may contain many aspects of a protocol. However, funding proposals may also lack specificity in analysis plans, procedures, measurements, instrumentation, and other key design considerations needed to carry out the study and potentially replicate it for independent verification of the results. Furthermore, funding proposals are not usually publicly available because the proposals may contain proprietary information.

In addition, a core principle of comparative effectiveness research, patient-centered outcomes research, and other forms of translational research is that collaborations between researchers and stakeholders should be formed so the outputs of research are relevant, applicable, and potentially useable for informing stakeholder decisions or actions. A study with a protocol developed through the guidance of accepted scientific standards is better served in minimizing the risk of biases, and it holds potential to produce more valid research. In addition, written guidance for protocol development helps facilitate communication between researchers and stakeholders so that they can work collaboratively to design new research in a way that protects against biases being introduced into the study design. The absence of standards for developing protocols may open opportunities for biases being introduced into study design either inadvertently or, however subtly, intentionally if researchers, stakeholders, or others have specific interests in directing research to favor certain outcomes.

The overall aims of this *Observational CER User's Guide* for the design of comparative effectiveness research protocols are to identify both minimal standards and best practices for designing observational comparative effectiveness research (CER) studies in the DEcIDE Network. In addition, other researchers who are not affiliated with the DEcIDE Network may also wish to use this *User's Guide* and adapt or expand upon the principles described in the document. CER is still a relatively new field of inquiry that has its origins across multiple disciplines, including health technology assessment, clinical research, epidemiology, economics, and health services research. Although the definition of CER and the body of work it represents is likely to evolve and be refined over time, a central focus that has emerged is the development of better scientific evidence on the effects of treatment on patient-centered health outcomes. For this version of the *User's Guide*, the definition of CER from the Institute of Medicine (IOM) report will be used.[22] The IOM report states that CER is the "generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve care both at the individual and the population levels."

The *User's Guide* was created over a period of approximately 2 years by researchers affiliated with AHRQ's EHC Program, particularly those in the DEcIDE Network. A goal was for investigators to articulate key considerations for observational CER study design within the DEcIDE Program to strengthen research in the program and improve the transparency of the methods that are applied. The *User's Guide* was modeled on similar AHRQ initiatives to publish methods guides for conducting comparative effectiveness systematic reviews[23] and patient registries.[24] Investigators worked together to write each of the chapters, which were subject to multiple internal and external independent reviews. All investigators had the opportunity to discuss, review, and comment on the recommendations that are provided in this document. Undoubtedly, new approaches to

research will develop, and the minimal standards of practice will change or evolve over time, necessitating periodic update of the *User's Guide.* Nonetheless, this document brings together the knowledge of the current DEcIDE Program researchers to begin laying the groundwork for writing better research protocols for observational CER studies.

To summarize, the goals for the *Observational CER User's Guide* are to:

- Support the development of scientifically rigorous observational research that produces valid new knowledge and reduces uncertainty about the effects of interventions on patient health outcomes.
- Increase the collaboration between researchers, patients, and other decisionmakers in designing valid studies that generate new scientific evidence for informing health care decisions.
- Increase the transparency of methodologies and study designs that are used in comparative effectiveness and patient-centered outcomes research.
- Improve the quality and consistency of research by eliminating or reducing inappropriate variation in the design of studies.
- Stimulate researchers and stakeholders to consider important principles when designing a comparative effectiveness study and writing a study protocol.

Summary and Conclusion

The *Observational CER User's Guide* serves as a resource for investigators and stakeholders when designing observational CER studies, particularly those with findings that are intended to translate into decisions or actions. The *User's Guide* provides principles for designing research that will inform health care decisions of patients and other stakeholders. Furthermore, it serves as a reference for increasing the transparency of the methods used in a study and standardizing the review of protocols through checklists provided in every chapter.

The *Observational CER User's Guide* draws from the literature and complements other guidance on conducting observational research.[25] However, it is unique in that it is focused on developing study protocols that lead to valid research findings relevant to the important health care decisions facing patients, providers, and policymakers. In addition, the authors of the *User's Guide* are researchers knowledgeable about the literature on methods for observational studies as well as about the technical and practical aspects of implementing observational CER studies. Nevertheless, as the first guidance for developing CER protocols, this document will need to be evaluated, tested, and revised over time before widespread adoption is recommended. Notwithstanding this caveat, researchers and their collaborators may wish to consider the principles discussed in the *User's Guide* when designing new observational CER studies, and may wish to specify the final study design in a written protocol that is publicly available.

Since the design of a new research study involves critical thinking, making important decisions, and accepting some limitations, the *Observational CER User's Guide* is intended to serve as a reference for researchers and stakeholders in thinking through the tradeoffs of key issues when designing a new research study. The *User's Guide* is not meant to be prescriptive and is one of many resources for designing CER and other observational studies that investigators and stakeholders should consult when designing an observational CER study. Examples of these other resources include the Good ReseArch for Comparative Effectiveness (GRACE) Principles,[26] the ISPE (International Society for Pharmacoepidemiology) Guidelines for Good Pharmacoepidemiology Practices,[27-28] the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,[29] the ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Good Research Practices reports,[30] the Guide on Methodological Standards in Pharmacoepidemiology by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP),[31] and Methodological Standards for Patient-Centered Outcomes Research by PCORI.[32] Ultimately, the research team is responsible for the validity and integrity of its final study design. As a result, the research team should bring together a variety of resources and expertise to design and execute an observational CER study.

The *User's Guide* was written with the intent of improving the overall quality of research in the DEcIDE Program and other similar observational research networks. The goal is to support the development of scientifically rigorous research that provides new knowledge for informing health care decisions and protects against bias being introduced into the research. As new research methods, standards, and statistical tools develop, this *User's Guide* will need to be periodically updated. It is hoped that researchers and stakeholders will find the *User's Guide* useful. Comments from investigators, stakeholders, and other users are welcome so they can be considered for incorporation into future versions of the *User's Guide*.

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